

EXHIBIT DD

The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction

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Abstract

Public health authorities have described, with growing alarm, an unprecedented increase in morbidity and mortality associated with use of opioid pain relievers (OPRs). Efforts to address the opioid crisis have focused mainly on reducing nonmedical OPR use. Too often overlooked, however, is the need for preventing and treating opioid addiction, which occurs in both medical and nonmedical OPR users. Overprescribing of OPRs has led to a sharp increase in the prevalence of opioid addiction, which in turn has been associated with a rise in overdose deaths and heroin use. A multifaceted public health approach that utilizes primary, secondary, and tertiary opioid addiction prevention strategies is required to effectively reduce opioid-related morbidity and mortality. We describe the scope of this public health crisis, its historical context, contributing factors, and lines of evidence indicating the role of addiction in exacerbating morbidity and mortality, and we provide a framework for interventions to address the epidemic of opioid addiction.

INTRODUCTION

Over the past 15 years, the rate of opioid pain reliever (OPR) use in the United States has soared. From 1999 to 2011, consumption of hydrocodone more than doubled and consumption of oxycodone increased by nearly 500% (42). During the same time frame, the OPR-related overdose death rate nearly quadrupled (15). According to the United States Centers for Disease Control and Prevention (CDC), the unprecedented increase in OPR consumption has led to the “worst drug overdose epidemic in [US] history” (58). Given the magnitude of the problem, in 2014 the CDC added opioid overdose prevention to its list of top five public health challenges (13).

Overdose mortality is not the only adverse public health outcome associated with increased OPR use. The rise in opioid consumption has also been associated with a sharp increase in emergency room visits for nonmedical OPR use (69) and in neonatal abstinence syndrome (57). Moreover, from 1997 to 2011, there was a 900% increase in individuals seeking treatment for addiction to OPRs (66, 68). The correlation between opioid sales, OPR-related overdose deaths, and treatment seeking for opioid addiction is striking (**Figure 1**).

Addiction is defined as continued use of a drug despite negative consequences (1). Opioids are highly addictive because they induce euphoria (positive reinforcement) and cessation of chronic use produces dysphoria (negative reinforcement). Chronic exposure to opioids results in structural and functional changes in regions of the brain that mediate affect, impulse, reward, and motivation (83, 91). The disease of opioid addiction arises from repeated exposure to opioids and can occur in individuals using opioids to relieve pain and in nonmedical users.

Another important feature of the opioid addiction epidemic is the relationship between OPR use and heroin use. According to the federal government’s National Survey on Drug Use and Health (NSDUH), 4 out of 5 current heroin users report that their opioid use began with OPRs (54). Many of these individuals appear to be switching to heroin after becoming addicted to OPRs because heroin is less expensive on the black market. For example, in a recent sample of

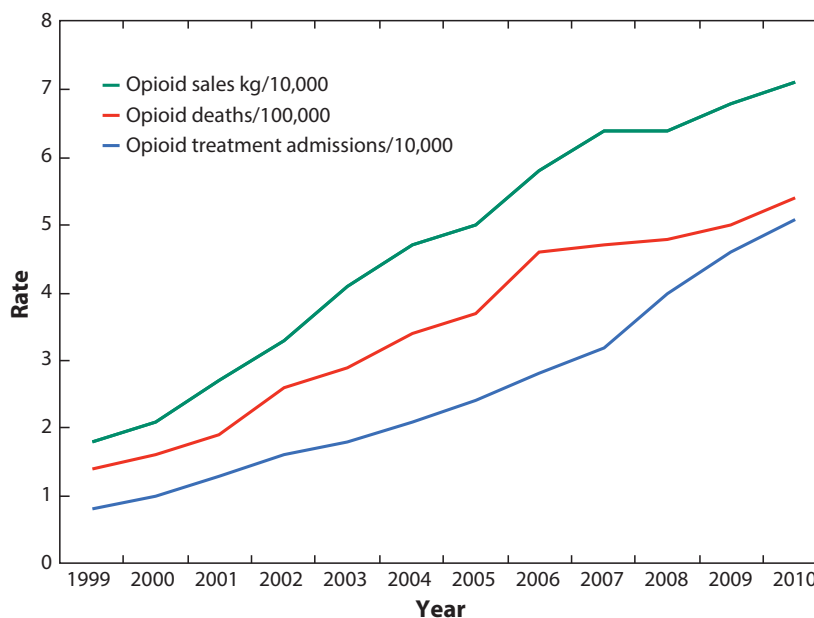


Figure 1

Rates of OPR sales, OPR-related unintentional overdose deaths, and OPR addiction treatment admissions, 1999–2010. Abbreviation: OPR, opioid pain reliever. Source: 10.

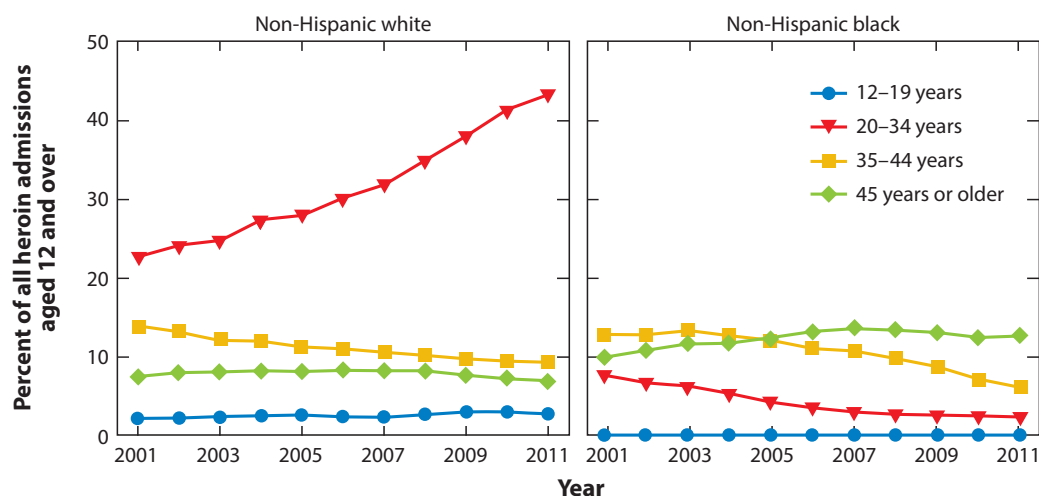


Figure 2

Heroin admissions, by age group and race/ethnicity: 2001–2011. Source: 68.

opioid-addicted individuals who switched from OPRs to heroin, 94% reported doing so because OPRs “were far more expensive and harder to obtain” (16, p. 24).

The increased prevalence of opioid addiction has also been associated with increases in heroin-related morbidity and mortality. For example, since 2001, heroin addiction treatment admissions for whites ages 20–34 have increased sharply (**Figure 2**). During this time frame, heroin overdose deaths among whites ages 18–44 increased by 171% (14).

HISTORY OF OPIOID ADDICTION IN THE UNITED STATES

The current opioid addiction crisis is, in many ways, a replay of history. America’s first epidemic of opioid addiction occurred in the second half of the nineteenth century. In the 1840s, the estimated national supply of opium and morphine could have supported a maximum of 0.72 opioid-addicted individuals per 1,000 persons (18). Over the next 50 years, opioid consumption soared by 538%. It reached its peak in the mid-1890s, when the supply could have supported a maximum of ~4.59 opioid-addicted individuals per 1,000 persons. The ceiling rate then began to decline, and by 1920 there were no more than 1.97 opioid-addicted individuals per 1,000 persons in the United States.

The epidemic had diverse origins. Mothers dosed themselves and their children with opium tinctures and patent medicines. Soldiers used opium and morphine to treat diarrhea and painful injuries. Drinkers alleviated hangovers with opioids. Chinese immigrants smoked opium, a practice that spread to the white underworld. But the main source of the epidemic was iatrogenic morphine addiction, which coincided with the spread of hypodermic medication during 1870–1895. The model opioid-addicted individual was a native-born white woman with a painful disorder, often of a chronic nature.

Nineteenth-century physicians addicted patients—and, not infrequently, themselves—because they had few alternatives to symptomatic treatment. Cures were scarce and the etiology of painful conditions was poorly understood. An injection of morphine almost magically alleviated symptoms, pleasing doctors and patients. Many patients continued to acquire and inject morphine, the sale of which was poorly controlled.

The revolutions in bacteriology and public health, which reduced diarrheal and other diseases commonly treated with opium; the development of alternative analgesics such as aspirin; stricter

prescription laws; and admonitions about morphine in the lay and professional literature stemmed the addiction tide. One important lesson of the first narcotic epidemic is that physicians were educable. Indeed, by 1919, narcotic overprescribing was the hallmark of older, less-competent physicians. The younger, better-trained practitioners who replaced them were more circumspect about administering and prescribing opioids (5).

For the rest of the twentieth century, opioid addiction epidemics resulted from transient increases in the incidence of nonmedical heroin use in urban areas. After World War II, these epidemics disproportionately affected inner-city minority populations, such as the large, heavily publicized increase in ghetto heroin use and addiction at the end of the 1960s (24, 37).

THE SHARP RISE IN PRESCRIPTION OPIOID CONSUMPTION

In 1986 a paper describing the treatment of 38 chronic pain patients concluded that OPRs could be prescribed safely on a long-term basis (61). Despite its low-quality evidence, the paper was widely cited to support expanded use of opioids for chronic non-cancer pain. Opioid use increased gradually in the 1980s. In 1996, the rate of opioid use began accelerating rapidly (38). This acceleration was fueled in large part by the introduction in 1995 of OxyContin, an extended release formulation of oxycodone manufactured by Purdue Pharma.

Between 1996 and 2002, Purdue Pharma funded more than 20,000 pain-related educational programs through direct sponsorship or financial grants and launched a multifaceted campaign to encourage long-term use of OPRs for chronic non-cancer pain (86). As part of this campaign, Purdue provided financial support to the American Pain Society, the American Academy of Pain Medicine, the Federation of State Medical Boards, the Joint Commission, pain patient groups, and other organizations (27). In turn, these groups all advocated for more aggressive identification and treatment of pain, especially use of OPRs.

For example, in 1995, the president of the American Pain Society introduced a campaign entitled “Pain is the Fifth Vital Sign” at the society’s annual meeting. This campaign encouraged health care professionals to assess pain with the “same zeal” as they do with vital signs and urged more aggressive use of opioids for chronic non-cancer pain (9). Shortly thereafter, the Veterans’ Affairs health system, as well as the Joint Commission, which accredits hospitals and other health care organizations, embraced the Pain is the Fifth Vital Sign campaign to increase the identification and treatment of pain, especially with OPRs. Similarly, the American Pain Society and the American Academy of Pain Medicine issued a consensus statement endorsing opioid use for chronic non-cancer pain (31). Although the statement cautioned against imprudent prescribing, this warning may have been overshadowed by assertions that the risk of addiction and tolerance was low, risk of opioid-induced respiratory depression was short-lived, and concerns about drug diversion and abuse should not constrain prescribing.

Prior to the introduction of OxyContin, many physicians were reluctant to prescribe OPRs on a long-term basis for common chronic conditions because of their concerns about addiction, tolerance, and physiological dependence (80). To overcome what they claimed to be “opiophobia,” physician-spokespersons for opioid manufacturers published papers and gave lectures in which they claimed that the medical community had been confusing addiction with “physical dependence.” They described addiction as rare and completely distinct from so-called “physical dependence,” which was said to be “clinically unimportant” (60, p. 300). They cited studies with serious methodological flaws to highlight the claim that the risk of addiction was less than 1% (28, 45, 52, 59, 62).

In addition to minimizing risks of OPRs, the campaign advanced by opioid manufacturers and pain organizations exaggerated the benefits of long-term OPR use. In fact, high-quality,

long-term clinical trials demonstrating the safety and efficacy of OPRs for chronic non-cancer pain have never been conducted. Surveys of patients with chronic non-cancer pain receiving long-term OPRs suggest that most patients continued to experience significant chronic pain and dysfunction (25, 76). The CDC and some professional societies now warn clinicians to avoid prescribing OPRs for common chronic conditions (29).

Although increased opioid consumption over the past two decades has been driven largely by greater ambulatory use for chronic non-cancer pain (8), opioid use for acute pain among hospitalized patients has also increased sharply. A recent study found that physicians prescribed opioids in more than 50% of 1.14 million nonsurgical hospital admissions from 2009 to 2010, often in high doses (34). The Joint Commission's adoption of the Pain is the Fifth Vital Sign campaign and federally mandated patient satisfaction surveys asking patients to rate how often hospital staff did "everything they could to help you with your pain" are noteworthy, given the association with increased hospital use of OPRs.

REFRAMING THE OPIOID CRISIS AS AN EPIDEMIC OF ADDICTION

Policy makers and the media often characterize the opioid crisis as a problem of nonmedical OPR abuse by adolescents and young adults. However, several lines of evidence suggest that addiction occurring in both medical and nonmedical users, rather than abuse per se, is a key driver of opioid-related morbidity and mortality in medical and nonmedical OPR users.

Opioid Harms Are Not Limited to Nonmedical Users

Over the past decade, federal and state policy makers have attempted to reduce OPR abuse and OPR-related overdose deaths. Despite these efforts, morbidity and mortality associated with OPRs have continued to worsen in almost every US state (10). Thus far, these efforts have focused primarily on preserving access to OPRs for chronic pain patients while reducing nonmedical OPR use (89), defined as the use of a medication without a prescription, in a way other than as prescribed, or for the experience or feeling it causes. However, policy makers who focus solely on reducing nonmedical use are failing to appreciate the high opioid-related morbidity and mortality in pain patients receiving OPR prescriptions for medical purposes.

The incidence of nonmedical OPR use increased sharply in the late 1990s, peaking in 2002 with 2.7 million new nonmedical users. Since 2002, the incidence of nonmedical use has gradually declined to ~1.8 million in 2012 (64, 70) (**Figure 3**). Although the number of new nonmedical users has declined, overdose deaths, addiction treatment admissions, and other adverse public health outcomes associated with OPR use have increased dramatically since 2002.

A comparison of age groups of nonmedical OPR users to age groups suffering the highest rates of opioid-related morbidity and mortality suggests that strategies focused exclusively on reducing nonmedical OPR use are insufficient (**Figure 4**). Although past-month nonmedical use of OPRs is most common in teenagers and young adults between the ages of 15 and 24 (65), OPR overdose deaths occur most often in adults ages 45–54, and the age group that has experienced the greatest increase in overdose mortality over the past decade is 55–64 (15), an age group in which medical use of OPRs is common. Opioid overdoses appear to occur more frequently in medical OPR users than in young nonmedical users. For example, in a study of 254 unintentional opioid overdose decedents in Utah, 92% of the decedents had been receiving legitimate OPR prescriptions from health care providers for chronic pain (39).

Middle-aged women and the elderly are more likely than other groups to visit doctors with complaints of pain (4). The development of iatrogenic opioid addiction in these groups may explain why they have experienced the largest increase in hospital stays resulting from opioid user

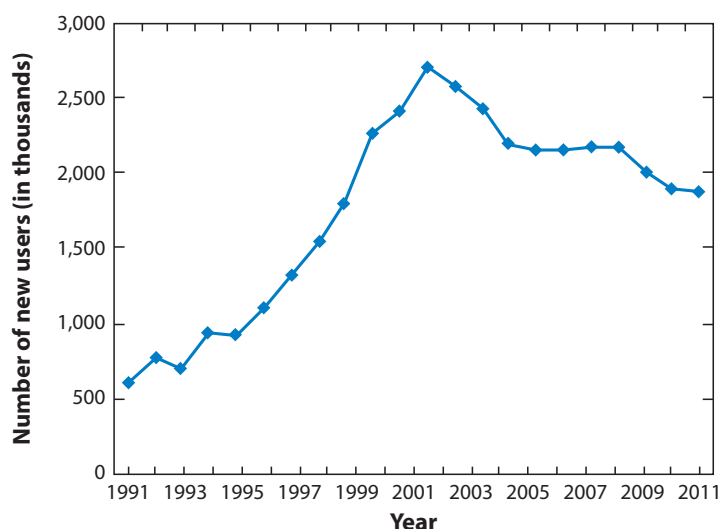


Figure 3

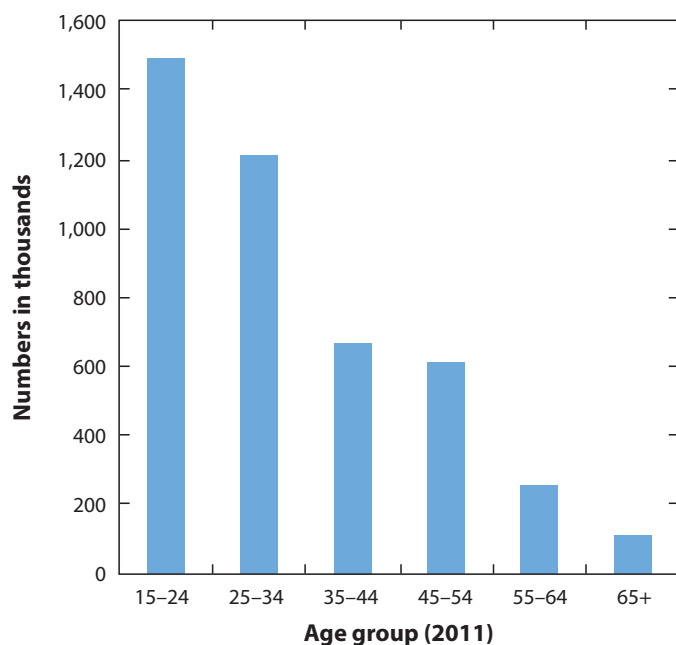
First-time nonmedical use of pain relievers. Source: 64, 70.

disorders since 1993 (56) (**Figure 5**). Over the past decade, white women ages 55–64 have also experienced the largest increase in accidental opioid overdose deaths (12, 15).

Opioid Addiction Is a Key Driver of Morbidity and Mortality

Accidental opioid overdose is a common cause of death in individuals suffering from opioid addiction (36). Although overdoses do occur in medical and nonmedical OPR users who are not

a Past month nonmedical OPR use by age



b OPR-related unintentional overdose deaths by age

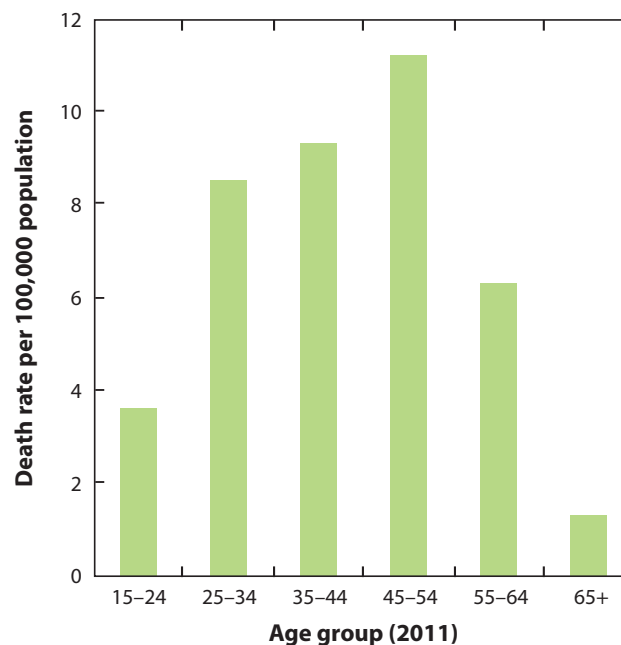


Figure 4

(a) Past month nonmedical OPR use by age versus (b) OPR-related unintentional overdose deaths by age. Abbreviation: OPR, opioid pain reliever. Sources: 58, 68.

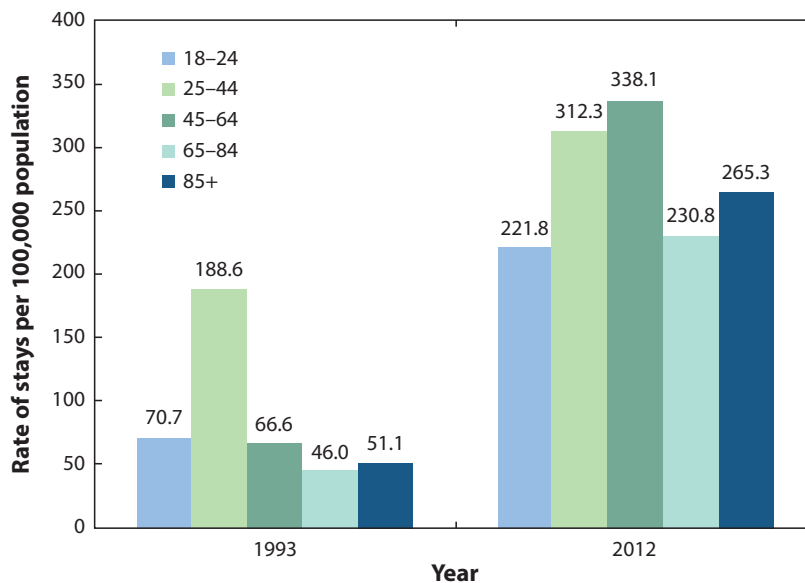


Figure 5

Rate of hospital inpatient stays related to OPR use by adult age group, 1993 and 2012. Source: 56.

opioid-addicted, consistent findings in samples of OPR overdose decedents show that deaths are most common in individuals likely to be suffering from opioid addiction. A study of 295 unintentional OPR overdose deaths in West Virginia found that four out of five decedents (80%) had a history of a substance use disorder (33). Another study found that among 254 opioid overdose decedents in Utah, about three-fourths (76%) had relatives or friends who were concerned about the decedent's misuse of opioids prescribed for pain (39).

The sharp increase in the prevalence of opioid addiction is a key driver of opioid-related morbidity and mortality. The misattribution of the opioid crisis to nonmedical use or abuse rather than to addiction has stymied efforts to address this crisis because it has led to a focus on policies to prevent such nonmedical use at the expense of greater resources committed to preventing and treating opioid addiction in both medical and nonmedical users.

PREVENTION STRATEGIES

This section organizes strategies for curbing the epidemic of opioid addiction into primary, secondary, and tertiary prevention. Although some specific interventions are discussed, we do not provide an exhaustive list. Rather, our purpose is to demonstrate that prevention strategies employed in epidemiologic responses to communicable and noncommunicable disease epidemics apply equally well when the disease in question is opioid addiction. Interventions should focus on preventing new cases of opioid addiction (primary prevention), identifying early cases of opioid addiction (secondary prevention), and ensuring access to effective addiction treatment (tertiary prevention).

Primary Prevention

The aim of primary prevention is to reduce the incidence of a disease or condition. Opioid addiction is typically chronic, life-long, difficult to treat, and associated with high rates of morbidity and mortality. Thus, bringing the opioid addiction epidemic under control requires effort to prevent new cases from developing.

Preventing addiction caused by medical exposure to OPRs. The incidence of iatrogenic opioid addiction in patients treated with long-term OPRs is unknown because adequately designed prospective studies have not been conducted. However, opioid use disorders appear to be highly prevalent in chronic pain patients treated with OPRs. A survey performed by Boscarino et al. of 705 chronic pain patients treated in specialty and primary care outpatient centers found that 26% met the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) IV criteria for opioid dependence, and 35% met DSM V criteria for an opioid use disorder (6, 7). A systematic review of studies utilizing opioids for low back pain found that aberrant drug abuse–related behaviors suggestive of addiction occurred in up to 24% of patients on long-term OPRs (50). Many patients on long-term OPRs worry about dependence and addiction and express a desire to taper or cease opioid therapy (76).

To reduce the incidence of iatrogenic opioid addiction, health care professionals must prescribe opioids more cautiously for both acute and chronic pain. Unfortunately, the campaign to encourage OPR prescribing has left many health care providers with a poor appreciation of opioid risks, especially the risk of addiction, and an overestimation of opioid benefits. Despite these risks and the lack of evidence supporting long-term efficacy, OPR prescribing for chronic non-cancer pain increased over the past decade while use of nonopioid analgesics decreased (20). This pattern highlights the need for prescriber education that explicitly corrects misperceptions about OPR safety and efficacy. If clinicians treating pain more often substituted nonopioid analgesics and nonpharmaceutical approaches for OPRs, evidence suggests the incidence of opioid addiction would decline and outcomes for patients with chronic non-cancer pain would improve.

Many prescribers are unaware that evidence of long-term effectiveness for OPRs is lacking and that risks, in addition to addiction, include respiratory depression leading to unintentional overdose death; serious fractures from falls (71, 77); hypogonadism and other endocrine effects that can cause a spectrum of adverse effects (88); increased pain sensitivity (2); chronic constipation and serious fecal impaction (81); and chronic dry mouth, which can lead to tooth decay (79). Providing prescribers with accurate information about opioid risks and benefits could result in more informed risk/benefit appraisals. Indeed, one of the lessons learned from the nineteenth-century opioid addiction epidemic was that physicians were educable. By the early 1900s, aggressive opioid prescribing had become the hallmark of older, less-competent physicians (5).

Several states, including Iowa, Kentucky, Massachusetts, Ohio, Tennessee, and Utah, have passed mandatory prescriber education legislation (89). In addition, the US Food and Drug Administration (FDA) is requiring manufacturers of extended release and long-acting OPRs to sponsor educational programs for prescribers. Unfortunately, some of these educational programs, including those required by the FDA, imply that OPRs are safe and effective for chronic non-cancer pain instead of offering prescribers accurate information about OPR risks and benefits (84). It remains unclear whether or not educational programs such as these will reduce OPR prescribing for common conditions where risks of use are likely to outweigh benefits.

Some opioid manufacturers have reformulated OPRs to make them more difficult to misuse through an intranasal or injection route. These so-called abuse-deterrent formulations (ADFs) may offer safety advantages over easily snorted and injected OPRs, but they do not render them less addictive. Opioid addiction, in both medical and nonmedical OPR users, most frequently develops through oral use (85). Some opioid-addicted individuals may transition to intranasal or injection use, but most continue to use OPRs orally (47). Thus, ADFs should not be considered a primary prevention strategy for opioid addiction.

In 2013, the New York City Department of Health and Mental Hygiene released emergency room guidelines on OPR prescribing (55). Recommendations included in the guidelines call for substituting nonopioid analgesics when possible, avoiding use of extended-release OPRs, and

limiting the supply to three days. Reducing patient exposure to OPRs and reducing the supply of excess OPRs in the homes of discharged patients may be effective strategies for preventing opioid addiction that can occur from both medical and nonmedical OPR use.

Preventing addiction caused by nonmedical exposure to OPRs. Individuals who use OPRs nonmedically are at risk for developing opioid addiction. Thus, efforts to reduce nonmedical use are an important primary prevention strategy. Adolescents and young adults who experiment with nonmedical use are most likely to obtain OPRs for free from friends or family members who had received a legitimate prescription (70). This information suggests that more cautious prescribing is required to prevent nonmedical use of excess OPRs. Unused OPRs in medicine chests should be immediately discarded or returned to a pharmacy, which became permissible in October 2014 after the Drug Enforcement Administration made a federal regulatory change (82).

Although OPRs have an abuse liability similar to that of heroin (17), they are commonly perceived as less risky. Seventy-three percent of eighth graders surveyed in 2013 perceived occasional use of heroin without a needle as high risk, but only 26% perceived occasional use of Vicodin as high risk (41). Eighth graders also perceived occasional Vicodin use as less risky than occasional marijuana use, less risky than smoking 1–5 cigarettes per day, and less risky than moderate alcohol use.

Individuals who perceive the risk of nonmedical OPR use to be low may be more likely to misuse OPRs. A 2004 survey found that college students who perceive a low level of risk from OPRs were 9.6 times more likely to use OPRs nonmedically, as compared with those who perceive these medications as harmful (3). Although the ability for causal inference from this type of cross-sectional survey is limited, this finding suggests that social marketing campaigns designed to increase perceived harmfulness of OPRs may be an effective prevention strategy.

Secondary Prevention

The aim of secondary prevention is to screen for a health condition after its onset but before it causes serious complications. Efforts to identify and treat opioid-addicted individuals early in the course of the disease are likely to reduce the risk of overdose, psychosocial deterioration, transition to injection opioid use, and medical complications.

Physicians are frequently the source of OPRs for opioid-addicted medical and nonmedical users (43). Contacts with medical professionals present valuable opportunities for early identification of opioid addiction. However, detection of opioid addiction in OPR users can be very difficult. Opioid-addicted chronic pain patients may demonstrate aberrant drug-related behaviors, such as presenting for early refills. However, some opioid-addicted pain patients, especially those prescribed high doses, may not demonstrate drug-seeking behavior. Opioid-addicted individuals receiving OPR prescriptions are often reluctant to disclose their concerns about addiction with prescribers because they fear being judged, being cut off from a legitimate supply, or being labeled as malingerers for feigning pain.

The difficulty of diagnosing opioid addiction in individuals motivated to conceal their condition suggests that prescribers should seek collateral information before prescribing OPRs. Urine toxicology can be used to verify a patient's self-reported drug ingestion history (53). However, urine toxicology of patients on long-term OPRs is not a reliable strategy for identifying opioid addiction. Urine toxicology cannot determine if a patient is taking extra doses or if a patient is using OPRs by an intranasal or injection route.

Opioid-addicted individuals may receive OPR prescriptions from multiple providers, a practice referred to as "doctor shopping." Doctor shoppers can be identified through use of state

prescription drug monitoring programs (PDMPs). Some state PDMPs send unsolicited reports to the medical providers of doctor shoppers. Research suggests that unsolicited reports increase prescribers' ability to detect opioid addiction, sometimes prompting actions such as coordinating care with other providers and modifying their own prescribing practices, as well as screening and referring for addiction treatment (78).

Prescribers in most states can consult their state PDMP before prescribing OPRs. PDMPs may be especially useful in emergency rooms and other settings where opioid-addicted individuals feign pain to obtain OPRs. Too often, however, patients identified as doctor shoppers are simply turned away, without hospital staff attempting to link these patients to addiction treatment services. Efforts must be made to help these clinicians understand that drug-seeking patients are suffering from the chronic, life-threatening disease of opioid addiction.

One challenge to PDMP effectiveness has been the low rate of provider use of these data (48). To increase prescriber utilization, Kentucky, Tennessee, and New York passed legislation mandating that prescribers check the PDMP before prescribing controlled substances. Data from these states indicate that PDMP utilization increased rapidly subsequent to the mandate, which correlated with declines in opioid prescribing (KY, TN, NY) and a sharp drop in visits to multiple providers (TN, NY) (35).

Tertiary Prevention

Tertiary prevention strategies involve both therapeutic and rehabilitative measures once a disease is firmly established. The goal of tertiary prevention of opioid addiction is to prevent overdose deaths, medical complications, psychosocial deterioration, transition to injection drug use, and injection-related infectious diseases. Doing so is accomplished mainly by ensuring that opioid-addicted individuals can access effective and affordable opioid addiction treatment.

Opioid addiction treatment. The need for opioid addiction treatment is great and largely unmet. According to the NSDUH, an estimated 2.1 million Americans are addicted to OPRs, and 467,000 are addicted to heroin (70). Unfortunately, these estimates exclude many opioid-addicted pain patients because NSDUH participants are told by surveyors that "we are only interested in your use of prescription pain relievers that were not prescribed for you or that you used only for the experience or feeling they caused" (67, p. 124).

In 2005, there were an estimated 10 million chronic pain patients receiving daily, long-term treatment with OPRs (8). The continuing increase in opioid consumption from 2005 to 2011 (42) suggests that the number may now exceed 10 million. Applying the prevalence estimates of DSM IV opioid dependence found by Boscarino et al. (6) in pain patients taking long-term opioids would indicate that an additional 2.5 million chronic pain patients may be opioid-addicted. Thus, the total number of Americans suffering from opioid addiction may exceed 5 million.

Treatment of opioid addiction includes pharmacotherapies and psychosocial approaches, including residential treatment, mutual-help programs (e.g., Narcotics Anonymous), and 12-Step treatment programs. These modalities may be used as stand-alone interventions or in combination with pharmacotherapy. Psychosocial opioid addiction treatment approaches show value and are an important treatment option (63). However, research with greater specificity and consistency is needed to better evaluate outcomes.

Pharmacotherapies for opioid addiction include agonist maintenance with methadone and partial-agonist maintenance with buprenorphine and antagonist treatment with naltrexone, which is available in a monthly injection. Methadone and buprenorphine work by controlling cravings. Naltrexone works by preventing opioid-addicted individuals from feeling the effects of opioids.

Naltrexone may be helpful in highly motivated and carefully selected patients. However, patients treated with naltrexone may be at increased risk of overdose death should relapse occur (23).

Multiple well-designed randomized controlled trials provide strong evidence that buprenorphine maintenance and methadone maintenance are safe and effective treatments for opioid addiction (30, 40, 46, 49, 74, 75). Both buprenorphine and methadone treatment are associated with reduced overdose risk and improved maternal and fetal outcomes in pregnancy (19, 44, 51, 72). Despite strong evidence supporting the use of buprenorphine and methadone, fewer than 1 million Americans are receiving these treatments (87).

Methadone poses a substantially greater risk of respiratory depression than does buprenorphine and can be obtained only from licensed opioid treatment programs (OTPs). The lack of OTPs in many communities presents a major challenge to expanding access to methadone. In contrast, buprenorphine, a partial opioid agonist, has a better safety profile than does methadone and can be prescribed in an office-based setting (26). Barriers to accessing buprenorphine include federal limits on the number of patients a physician may treat, ineligibility of nurse practitioners to prescribe it, and inadequate integration of buprenorphine into primary care treatment. Access to buprenorphine treatment could be expanded if the federal government eased or remove regulatory barriers.

Harm-reduction approaches. Tertiary prevention strategies also include harm-reduction approaches to improving health outcomes and reducing overdose deaths. In the subset of opioid-addicted individuals who are heroin injection drug users, evidence suggests that access to syringe exchange programs can prevent HIV infection (22). These efforts have been less effective at preventing hepatitis C infection, which is increasing rapidly in young, white IDUs (32).

Expanding access to naloxone, an opioid overdose antidote, can prevent overdose deaths by reversing life-threatening respiratory depression. In the 1990s, syringe exchange programs began distributing naloxone to injection drug users for the purpose of rescuing peers. Evidence shows that clients of syringe exchange programs demonstrated the ability to successfully reverse overdoses when they had been provided with naloxone and training (73). In addition, providing family members of opioid-addicted individuals and nonparamedic first responders with naloxone may be an effective strategy for rescuing overdose victims (21, 90). At present, there are more than 188 community-based naloxone distribution programs in 15 states and the District of Columbia (11).

CONCLUSION

The increased prevalence of opioid addiction, caused by overprescribing of OPRs, has led to a parallel increase in opioid overdose deaths. Efforts to address this crisis that focus exclusively on reducing nonmedical OPR use have been ineffective. Middle-aged and elderly individuals commonly exposed to OPRs for pain treatment have experienced the largest increase in rates of opioid-related morbidity and mortality. Recognition that opioid addiction in both medical and nonmedical users is a key driver of opioid-related morbidity and mortality will result in a more effective response to this public health crisis. Just as public health authorities would approach other disease outbreaks, efforts must be made to reduce the incidence of opioid addiction, identify cases early, and ensure access to effective treatment.

Preventing opioid addiction requires strategies that foster more cautious and selective OPR prescribing. However, if prescribing is reduced without also ensuring access to addiction treatment, the opioid overdose death rate may remain at a historically high level and the use of heroin may continue to increase. Coordinated efforts from federal agencies, state agencies, health care insurers, and health care providers are required to address the needs of millions of Americans now struggling with this chronic, life-threatening disease.

DISCLOSURE STATEMENT

Dr. Alexander is Chair of the FDA's Peripheral and Central Nervous System Advisory Committee, serves as a paid consultant to IMS Health, and serves on an IMS Health scientific advisory board. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Ms. Hwang is a current ORISE Fellow at the FDA.

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